## REMARKS/ARGUMENTS

Claims 1-86 are pending in the present application. Claims 1-32 are canceled and claims 33-52 and 54-56 are withdrawn as being drawn to a nonelected invention. Claim 53 is amended. No new matter is added by this amendment. Entry of this amendment is respectfully requested.

**With Respect to the Rejections under 35 U.S.C. §102, Pages 2-4 of the Office Action:**

Claim 53 is rejected under 35 §102(e) as being anticipated by Jacobsen et al. (US 2005/0272075) for the reasons set forth on pages 2-4 of the Office Action. Applicant respectfully traverses the rejection because the Office has failed to provide a *prima facie* case of anticipation.

As a preliminary matter, the rejection set forth on pages 2-4 of the Office Action appears to be directed to nonelected claim 52 rather than the currently elected claim, claim 53. The Office Action states that "Jacobsen et al. teach methods for isolating microRNA of interest, the method comprising providing a first and second capture probe having identical second adaptor segment sequences ..." However, claim 53 recites "the first capture probe has a first adaptor segment sequence that is different from the first adaptor segment sequence of the second capture probe."

Applicant respectfully submits that the Jacobsen et al. reference does not anticipate the claimed invention. As set forth in MPEP 2131: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

The claimed invention is directed to a method for isolating a microRNA of interest from a sample, using a first and second capture probe, by combining the sample, the capture probes, a

first linker and the second linker, and ligating the 3' end of the first linker to the 5' end of the microRNA of interest and the 3' end of the microRNA of interest to the 5' end of the second linker, thereby producing a ligated strand comprising a first linker, a microRNA of interest and a second linker hybridized to the capture probe. Jacobsen et al. discloses methods for isolating a microRNA that may include a ligation reaction. However, the ligation reactions taught by Jacobsen et al. are distinguishable from the claimed invention.

**The capture probe of Jacobsen et al. is not the same as the capture probes of the claimed invention:**

The claimed invention includes the step of "providing a capture probe." Jacobsen et al. define a "capture probe" as follows:

> [0072] The term "Capture probes" or "capture probe" refer to a probe(s), comprising a recognition sequence, complementary to the target sequence, e.g. a short RNA target sequence, and an anchor sequence essential for subsequent capture, reverse transcription reaction, or amplification by PCR. The anchor sequence function as priming sites for the RT- or PCR primers in subsequent reverse transcription reaction, real-time PCR, or as tags for capture assays.

See, also: page 16, paragraphs [0145]-[0164], which describe Figs. 27 & 28, i.e., the use of a capture probe to immobilize and enrich for a target sequence before performing reverse transcriptase and primer extension reactions. As set forth in claim 33, a capture probe in accordance with the claimed invention comprises:

> i) a first adapter segment having a first adapter segment sequence, the first adapter segment comprising a 3' end and a 5' end;
>
> ii) a second adapter segment having a second adapter segment sequence, the second adapter segment comprising a 3' end and a 5' end; and
>
> iii) a microRNA binding segment having a microRNA binding segment sequence;
>
> where the microRNA binding segment is substantially complementary to, and capable of hybridizing to, one or more than one microRNA of interest by Watson-Crick base pairing;

where the 5' end of the first adapter segment is connected to the 3' end of the microRNA binding segment; and

where the 3' end of the second adapter segment is connected to the 5' end of the microRNA binding segment;

The "capture probe" of Jacobsen et al. can be distinguished from the first and second capture probes of the claimed invention because it does not expressly or inherently include both first and second adapter segments, which are connected to both the 3' and 5' ends of the microRNA binding segment/recognition sequence.

**A "linker" as defined in Jacobsen et al. is not the same as the first and second linkers of the claimed invention:**

The claimed invention includes the step of "providing a first linker and a second linker." Jacobsen et al. define a "linker" as follows:

> [0073] In the present context, the term "linker" means a thermochemically and photochemically non-active distance-making group that is used to join two or more different nucleotide moieties of the types defined above. ... The linker, thus, comprises a chain of carbon atoms optionally interrupted or terminated with one or more heteroatoms, such as oxygen atoms, nitrogen atoms, and/or sulphur atoms. Thus, the linker may comprise one or more amide, ester, amino, ether, and/or thioether functionalities, and optionally aromatic or mono/polyunsaturated hydrocarbons, polyoxyethylene such as polyethylene glycol, oligo/polyamides such as poly-(3-alanine, polyglycine, polylysine, and peptides in general, oligosaccharides, oligo/polyphosphates. Moreover the linker may consist of combined units thereof. ...

As set forth in claim 33, the characteristics of a first linker, in accordance with the claimed invention, include:

where the first linker has a first linker sequence, and comprises a 3' end and a 5' end; where the first linker is substantially complementary to, and capable of hybridizing to, the first adapter segment of the capture probe by Watson-Crick base pairing.

Likewise, the characteristics of a second linker, in accordance with the claimed invention, include:

> where the second linker has a second linker sequence, and comprises a 3' end and a 5' end; and where the second linker is substantially complementary to, and capable of hybridizing to, the second adapter segment of the capture probe by Watson-Crick base pairing.

Moreover, as set forth on page 9, lines 4-7 of the present application:

> In one embodiment, the first linker segment and the second linker segment comprise a substance selected from the group consisting of one or more than one type of polynucleotide, one or more than one type of polynucleotide analog, and a combination of one or more than one type of polynucleotide and polynucleotide analog

Accordingly, a "linker" as defined by Jacobsen et al. can be distinguished from the first and second linkers of the present invention because it does not expressly or inherently comprise a 3' and a 5' end, nor is it expressly or inherently substantially complementary to, and capable of hybridizing to any other segment of the capture probe.

**The first and second tagging probes of Jacobsen et al. are not the same as the first and second capture probes of the claimed invention:**

According to the Office Action, "Jacobsen et al. teach methods for isolating microRNA of interest, the method comprising providing a first and second capture probe." Jacobsen et al. do teach methods for detecting a microRNA using a first and a second "tagging" probe. However the tagging probes of Jacobsen et al. are structurally and functionally distinct from the capture probes of the claimed invention.

Embodiment #1

Jacobsen et al. describes one pair of tagging probes that are used for RNA-templated ligation reactions. For example, see page 9 paragraph [0084] for a definition of "two tagging probes" or "a pair of tagging probes:" These first and second tagging probes are unlike the first and second capture probes of the claimed invention because they do not expressly or inherently include both first and second adapter segments, which are connected to both the 3' and 5' ends of the microRNA binding segment/recognition sequence. Moreover "the recognition sequence of the first tagging probe hybridizes to a first region within a target sequence and the recognition sequence of the second tagging probe hybridizes to a second region within the same

complementary target sequence." To further distinguish the first and second capture probes of the claimed invention, claim 53 is amended to clarify that "the first capture probe has a microRNA binding segment sequence that binds to a microRNA of interest that is different from the microRNA binding segment sequence and the microRNA of interest of the second capture probe."

Embodiment #2

Jacobsen et al. describes an alternative version of the first and second tagging probes that are used as primers for reverse transcription or primer extension reactions. See, e.g. page 5 paragraph [0029], page 9 paragraphs [0085] and [0086], and page 16 paragraphs [0162] and [0163]. In this alternative embodiment only the first tagging probe, i.e., the RT tagging probe, contains a recognition sequence that is complementary to the target microRNA. The RT tagging probe is used to prime a reverse transcriptase reaction. The recognition sequence of the 2nd tagging probe is complementary to the reverse transcriptase-extended nucleotide sequence corresponding to the 5'-end of the mature microRNA. Accordingly, this version of the first and second tagging probes is distinguishable from the first and second capture probes of the claimed invention.

**The microRNA-templated ligation reactions of Jacobsen et al. are not the same as the ligation reaction of the claimed method:**

According to the Office Action, "Jacobsen et al. teach methods for isolating microRNA of interest, the method comprising .... combining the sample, the capture probe, first and second linkers, allowing the first linker to hybridize with the first adapter segment, the microRNA to hybridize with the microRNA binding segment, the second linker to hybridize with the second adapter segment, ligating the 3' end of the first linker (which is hybridized to the first adapter segment) to the 5' end of the microRNA of interest (which is hybridized to the microRNA binding segment), ligating the 3' end of the microRNA of interest (which is hybridized to the microRNA binding segment to the 5' end of the second linker (which is hybridized to the second adaptor segment), dehybridizing the capture probe from the ligated strand, wherein the first linker binds to a substantially complementary first adapter segment of the capture probe, and the

second linker hybridizes to a substantially complementary second adapter segment of the capture probe." Jacobsen et al. do teach methods for detecting a microRNA using a first and a second "tagging" probe. For example, see page 4 paragraph [0027], page 9 paragraph [0084], page 10 paragraphs [0097] and [0098], page 15 paragraphs [0143] and [0144], page 27 paragraphs [0305] and [0306], page 30 paragraphs [0348] and [0349], and claim 4. This ligation reaction uses the microRNA of interest as a template for ligating two tagging probes. In contrast the claimed invention uses a capture probe as a template for ligating linkers to the microRNA of interest.

**The bridging probe of Jacobsen et al. can be distinguished from the capture probe of the claimed invention:**

As set forth on page 18 paragraph [0184] of Jacobsen et al.:

> [0184] Another means of appending additional sequence may be that of a ligation reaction. In such a reaction, an adaptor nucleic acid sequence may be attached to either the 3'-end, the 5'-end or both ends of the microRNA molecule by means of a ligation reaction. Such ligation reaction may be assisted by providing a "bridging" nucleic acid sequence comprising a nucleotide sequence specific for a terminal part of a mature target RNA sequence and a nucleotide sequence specific for terminal part of said adapter molecule such that the mature RNA target and said adaptor molecule are place in close vicinity to each other upon sequence specific hybridisation.

See, also, claim 24. The "bridging" nucleic acid sequence can be distinguished from the capture probe of the claimed invention because Jacobsen et al. does not explicitly or inherently disclose a "bridging" nucleic acid that includes "adaptor" segments that bring the microRNA in close vicinity to first and second linkers on both the 5' and 3'end.

**The use of a template polynucleotide as disclosed in Jacobsen et al. can be distinguished from the use of the capture probe of the claimed invention:**

Page 19 paragraph [0188] (and claim 10) of Jacobsen et al. discloses a method for quantitative determination of a short length RNA using "a template polynucleotide which consists of 1) a single stranded target sequence consisting of the sequence of said short-length RNA, its corresponding DNA sequence or a nucleotide sequence complementary to the sequence of said short-length RNA and 2) a 5' and/or a 3' adjacent nucleotide sequence. The template

polynucleotide, as broadly describe by Jacobsen et al. could encompass a capture probe as set forth in claim 33. However, as set forth in paragraphs [0189] and [0190], the Jacobsen et al. reference further discloses:

> [0189] b) using said template polynucleotide in a reverse transcription or a nucleotide polymerization to obtain a strand of cDNA, and
>
> [0190] c) performing a quantitative real-time PCR (qPCR) including as template(s) said cDNA and optionally the template polynucleotide.

In contrast, the claimed invention uses a capture probe as a template for a ligation reaction.

**Jacobsen et al. does not teach all of the limitations of claim 53:**

In addition to the forgoing distinctions between the methods of Jacobsen et al. and the claimed method, there is no teaching or suggestion anywhere in Jacobsen et al. of the following limitations set forth in claim 53:

- where the first capture probe has a first adapter segment sequence that is different from the first adapter segment sequence of the second capture probe;
- where the first capture probe has a microRNA binding segment sequence that binds to a microRNA of interest that is different from the microRNA binding segment sequence and the microRNA of interest of the second capture probe; and
- where the first capture probe has a second adapter segment sequence that is different from the second adapter segment sequence of the second capture probe.

Consequently, Applicant respectfully submits that the claimed method is not anticipated by the Jacobsen et al. reference.

The Applicant requests that the Examiner rejoin all non-elected claims if claim 53 as amended is found to be patentable.

**CONCLUSION**

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicant's representative.

If an extension of time is required to extend the time for filing a reply in the above-identified application, such extension is hereby requested.

The Director is hereby authorized to charge any fees which may be required to Deposit Account No. 19-2090.

Respectfully submitted,

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